CHEST

Effect of Ultrashort-Acting β-Blockers on Mortality in Patients With Sepsis With Persistent Tachycardia Despite Initial Resuscitation

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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BACKGROUND: Historically, β-blockers have been considered to be relatively contraindicated for septic shock because they may cause cardiac suppression. On the other hand, there is an increasing interest in the use of β-blockers for treating patients with sepsis with persistent tachycardia despite initial resuscitation.

RESEARCH QUESTION: Do ultrashort-acting β-blockers such as esmolol and landiolol improve mortality in patients with sepsis with persistent tachycardia despite initial resuscitation?

STUDY DESIGN AND METHODS: This was a systematic review and meta-analysis. We searched MEDLINE, Cochrane Central Register of Controlled Trials, and Embase for randomized controlled trials (RCTs) that compared the mortality of patients with sepsis and septic shock treated with esmolol or landiolol. We updated our search on April 20, 2020. Two independent reviewers assessed whether titles and abstracts met the following eligibility criteria: (1) RCT, (2) patients with sepsis and septic shock ≥ 18 years of age, and (3) treatment with either esmolol/landiolol or placebo/no interventions. Two authors independently extracted selected patient and study characteristics and outcomes. The results of all analyses are presented using random effect models.

RESULTS: Seven RCTs with a pooled sample size of 613 patients were included. Of these, six RCTs with 572 patients reported 28-day mortality. Esmolol or landiolol use in patients with sepsis and septic shock was significantly associated with lower 28-day mortality (risk ratio, 0.68; 95% CI, 0.54-0.85; $P < .001$). Unimportant heterogeneity was observed ($I^2 = 31\%$). The absolute risk reduction and number of patients to be treated to prevent one death were 18.2% and 5.5, respectively.

INTERPRETATION: The use of ultrashort-acting β-blockers such as esmolol and landiolol in patients with sepsis with persistent tachycardia despite initial resuscitation was associated with significantly lower 28-day mortality.

TRIAL REGISTRY: UMIN Clinical Trials Registry; No.: UMIN000040174; URL: https://www.umin.ac.jp/ctr/index.htm;

CHEST 2021; 159(6):2289-2300

KEY WORDS: β-blocker; esmolol; landiolol; sepsis; sepsis-associated tachycardia

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ABBREVIATIONS: APACHE II = Acute Physiology and Chronic Health Evaluation II; ARR = absolute risk reduction; HR = heart rate; MAP = mean arterial pressure; NNT = number needed to treat; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; SVI = stroke volume index

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Take-home Points

Study Question: Are ultrashort-acting β-blockers such as esmolol and landiolol effective in reducing the mortality in patients with sepsis with persistent tachycardia despite initial resuscitation?

Results: In this systematic review and meta-analysis of randomized controlled trials, the use of esmolol or landiolol in patients with sepsis with persistent tachycardia despite initial resuscitation was associated with significantly lower 28-day mortality with a risk ratio of 0.68.

Interpretation: Ultrashort-acting β-blockers such as esmolol and landiolol should be considered for the management of patients with sepsis with persistent tachycardia despite initial resuscitation.

Sepsis is a dysregulated inflammatory host response to an infection and often causes cardiovascular failure including tachycardia.[1] Tachycardia including atrial fibrillation is known to be associated with a higher mortality rate in patients with sepsis and septic shock.[2-4] Because tachycardia compromises the hemodynamics in patients with sepsis, it is important to select an appropriate strategy to manage tachycardia. A successful reduction in heart rate within the first 24 h in patients with septic shock is associated with an improved outcome.[2] Therefore, an adequate and prompt control of tachycardia in sepsis is crucial for improving treatment outcome. Among the several options for the management of tachycardia, there is an increasing interest in the use of β-blockers for treating sepsis and septic shock. In particular, there has been an increased focus on esmolol and landiolol, which are ultrashort-acting highly selective β1-blockers.

Historically, β-blockers have been considered to be relatively contraindicated for septic shock because they may cause cardiac suppression. The use of β-blockers in patients with sepsis was first described in 1969.[5] Since then, several experimental studies have been conducted on the use of β-blockers in sepsis treatment. Moreover, because of their hemodynamic effects, β-blockers are expected to improve the sepsis-induced hypermetabolic state, attenuate sepsis-induced cardiac dysfunction, and improve sepsis-induced coagulopathy.[6] Previous clinical studies have mainly investigated the heart rate (HR) reduction by esmolol or landiolol in patients with sepsis with persistent tachycardia despite initial resuscitation because these β-blockers are ultrashort acting and relatively safer than other longer-acting β-blockers. In most of these studies, mortality was set as a secondary outcome, and it remains controversial whether esmolol or landiolol improves mortality in addition to HR reduction. Therefore, there is a need to summarize the available evidence regarding the effect of esmolol or landiolol use on mortality in patients with sepsis with persistent tachycardia. We aimed to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effect of ultrashort-acting β-blockers, esmolol/landiolol, on mortality in patients with sepsis with persistent tachycardia despite initial resuscitation.

Methods

Protocol Registration

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7] The protocol was registered in the UMIN Clinical Trials Registry (https://www.umin.ac.jp) on April 20, 2020 (identification No.: UMIN000040174).

Search Strategy

A comprehensive search of the following three major databases was performed on April 20, 2020: MEDLINE (source: PubMed, 1966 to April 2020), Cochrane Central Register of Controlled Trials (through April 2020), and Embase (1974 to April 2020). The following key words were used in each search: esmolol, landiolol, adrenergic β-antagonists, sepsis, systemic inflammatory response syndrome, and multiple organ failure. Specific information about the search strategies and results is provided in e-Table 1.

Study Selection and Inclusion Criteria

We stored citations and removed duplicates using EndNote software (Thomson Reuters). The abstracts and titles of the studies were screened by two independent reviewers (D. H. and R. S.). For inclusion, the full text of these study articles was subsequently reviewed using Rayyan.[8] Disagreements between the reviewers were resolved by further discussion until a consensus was reached. We contacted the authors of the included trials to verify unclear information when necessary. There were no language restrictions, and we used Google Translate for non-English articles to minimize selection bias.[9,10] We included trials with the following characteristics: (1) study type: RCT; (2) patient population: patients ≥ 18 years of age with sepsis based on Sepsis-1,[11] Sepsis-2,[12] or Sepsis-3 definitions[13]; (3) intervention: IV esmolol or landiolol administration at any dose; and (4) control group: placebo or no intervention (no esmolol or landiolol administration).

(K. Takahashi), M&D Data Science Center, Tokyo Medical and Dental University, Tokyo, Japan.

Drs Hasegawa and Sato contributed equally to this manuscript.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: https://doi.org/10.1016/j.chest.2021.01.009

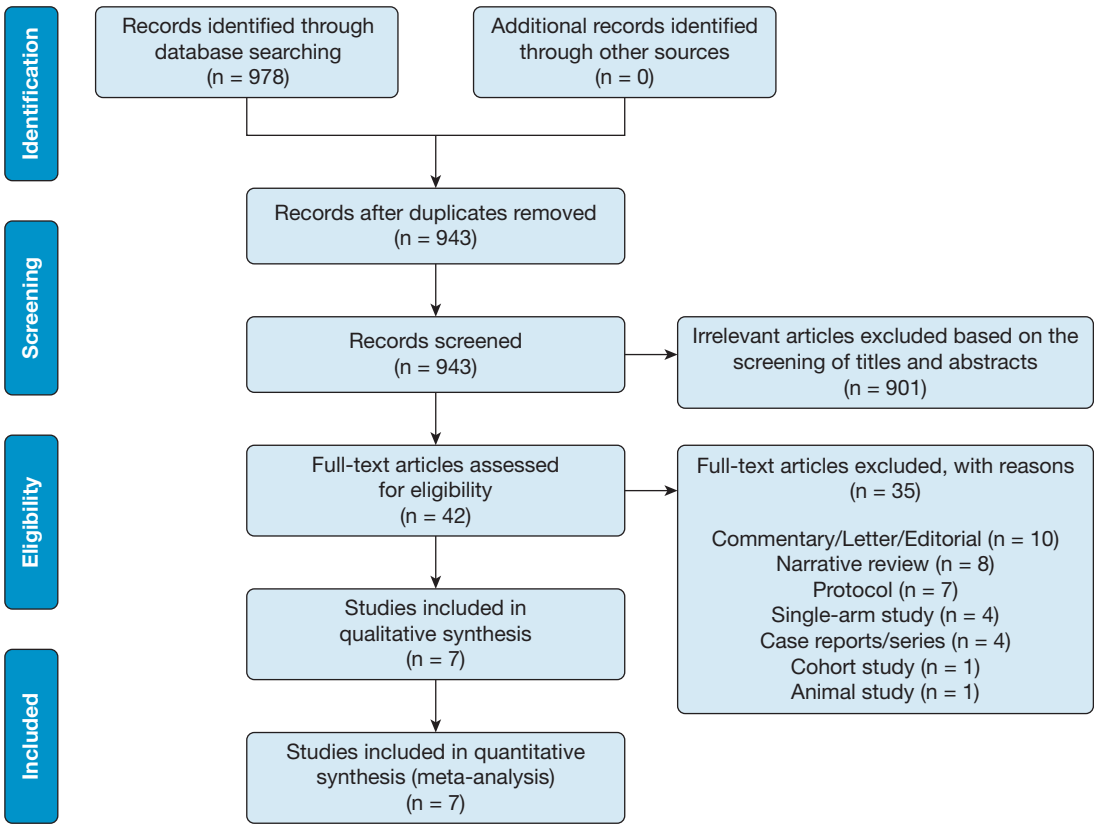
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 978)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 943)
Records screened (n = 943)
Irrelevant articles excluded based on the screening of titles and abstracts (n = 901)
Full-text articles assessed for eligibility (n = 42)
Full-text articles excluded, with reasons (n = 35)
Commentary/Letter/Editorial (n = 10)
Narrative review (n = 8)
Protocol (n = 7)
Single-arm study (n = 4)
Case reports/series (n = 4)
Cohort study (n = 1)
Animal study (n = 1)
Studies included in qualitative synthesis (n = 7)
Studies included in quantitative synthesis (meta-analysis) (n = 7)

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart: identification and selection of studies for inclusion.*

Data Extraction

Data were extracted using a standardized data extraction form by two independent reviewers (D. H. and R. S.), and disagreements were resolved by further discussion. When there were multiple publications by the same investigators, the reviewers assessed these publications carefully and contacted the investigators to ensure that no duplicate data were analyzed. We collected the following information for each study: first author's name, year of publication, country, definition of sepsis, patients' characteristics (eg, age, sex, Acute Physiology and Chronic Health Evaluation II [APACHE II] score), norepinephrine dose at baseline, 28-day mortality, sources of infection, inclusion and exclusion criteria, dose of esmolol or landiolol, and follow-up duration.

The primary outcome was 28-day mortality. The secondary outcomes were lactic acid levels at baseline and 24, 48, and 72 h after enrollment; HR; mean arterial pressure (MAP); norepinephrine dose; cardiac index; stroke volume index (SVI); and WBC count at 24 h after enrollment.

Bias Risk in Individual Trials

The methodologic quality of the studies was assessed by independent reviewers (D. H. and R. S.) to determine the risk of bias. Disagreements were resolved by further discussions. When it was difficult to reach a conclusion, a third reviewer (N. P.) also reviewed the full article and participated in the discussion. The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials was used to evaluate the risk of bias of each trial.[14,15]

Statistical Analysis

We performed statistical analyses using Mantel-Haenszel random effect models for binary outcomes and inverse-variance random effect models for continuous outcomes. The risk ratio (RR) or standardized mean difference (SMD) is expressed as point estimates with 95% CI and P value. For the data shown as median and interquartile range, median and interquartile range were converted to mean and SD[16] to obtain pooled RR and SMD. All RRs expressed the risk of 28-day mortality for the esmolol or landiolol group in comparison with that for the control group. Absolute risk reduction (ARR) and number needed to treat (NNT) were also calculated. We investigated statistical heterogeneity using the Mantel-Haenszel χ^2 test and I^2 statistic as the proportion of total variability explained by heterogeneity.[17] We predefined substantial heterogeneity with $P < .10$ in the Mantel-Haenszel χ^2 test or $I^2 > 50\%$.

Sensitivity analyses were performed to examine the robustness of the main results according to the severity of illness (ie, mortality rate of the control group [$< 66\%$ or $\geq 66\%$] and sample size [< 100 or ≥ 100]). To evaluate publication bias, we created funnel plots for 28-day mortality in which we plotted the log RRs against their SEs and tested the symmetry of the funnel plots using both Begg rank correlation test and Egger linear regression test. We performed all statistical analyses and assessed the risk of bias of each trial using RevMan Version 5.3 (The Cochrane Collaboration) and Stata software, V.14.0 (StataCorp) as appropriate. $P < .05$ was set as the level of statistical significance.

TABLE 1] Characteristics of Each Study

Study	Country	Sample Size	Setting	Study Period	Definition of Sepsis	Intervention	Primary Outcome (Secondary Outcome)	Administration of Esmolol/Landiolol
Kakihana et al[23]	Japan	151	Multicenter	January 2018 to April 2019	Sepsis-3	Landiolol vs none	Proportion of patients with HR of 60-94 beats/min 24 h after randomization (28-d mortality, proportion of patients with a decrease of ≥ 20%, proportion of patients whose HR was controlled to 60-94 beats/min up to 96 h, proportion of patients with new-onset Afib, clinically relevant hemodynamic and organ function markers, norepinephrine dosages, and adverse events)	Administration of landiolol: landiolol was initiated within 2 h after randomization that was conducted after being resuscitated with fluid and vasopressors. Mean time ± SD from entering ICU to randomization was 15.8 ± 13.4 h in the landiolol group and 13.5 ± 12.6 h in the control group. Initial dose of landiolol: initiated at 1 μg/kg/min. Titration or tapering: by 1 μg/kg/min generally every 15-20 min, until the HR decreased to < 95 beats/min. Duration of administration: landiolol was continued for at least 96 h after randomization. It was optional between 96 and 168 h after randomization.
Liu et al[21]	China	100	Single center	June 2016 to August 2017	Sepsis-2	Esmolol vs none	28-d mortality; 7-, 60-, and 90-d mortalities; HR; lactic acid level; inflammatory marker; APACHE II score; SOFA score; length of hospital stay; and duration of mechanical ventilation[a]	Administration of esmolol: initiated after randomization that was performed after being resuscitated with fluid and vasopressors for 24 h. Initial dose of esmolol: initiated at 25 mg/h. Titration or tapering: by 50 mg/h every 20 min to reach HR between 80 and 100 beats/min within 12 h. Permitted maximum dose was 0.3 mg/kg/min. Duration of administration: esmolol was continued until day 7, ICU discharge, or death.
Wang et al[20]	China	76	Single center	August 2011 to October 2016	Sepsis-2	Esmolol vs placebo (normal saline)	28-d mortality, cardiac output, MAP, CI, SVI, inflammatory markers, hemodynamics, and organ function markers[a]	Administration of esmolol: initiated after randomization that was performed after resuscitation with fluid and vasopressors for 24 h. Initial dose of esmolol: initiated at 3 mg/kg/min.[b] Titration or tapering: by 50 mg/h every 5 min to reach HR of < 95 beats/min within 4 h. Minimum

(Continued)

TABLE 1] *(Continued)*

Study	Country	Sample Size	Setting	Study Period	Definition of Sepsis	Intervention	Primary Outcome (Secondary Outcome)	Administration of Esmolol/Landiolol
								maintenance dose was 3 mg/kg/min. Permitted maximum dose was 12 mg/kg/min.[b] Duration of administration: esmolol was continued for 24 h.
Xinqiang et al[18]	China	48	Single center	September 2013 to September 2014	Sepsis-2	Esmolol vs none	28-d mortality, length of ICU stay (hemodynamic parameters such as HR, MAP, CVP, CI, SVI, and SVRI, and tissue oxygen metabolism markers such as $ScvO_2$ and lactic acid level)	Administration of esmolol: initiated after randomization that was performed after resuscitation with fluid and vasopressors for 6 h. Initial dose of esmolol: initiated at 0.05 mg/kg/min. Titration or tapering: adjusted to reach HR of $<$ 100 beats/min within 24 h. Permitted maximum dose was not specified. Duration of administration: not reported.
Wang et al[19]	China	60	Single center	June 2013 to June 2014	Sepsis-2	Esmolol and milrinone vs none	Reduction in HR to 75-94 beats/min over a 96-h period (28-d survival rate, hemodynamic and organ function variables, myocardial injury markers, serum proinflammatory markers, norepinephrine dosages, and adverse events)	Administration of esmolol: not reported. Initial dose of esmolol: not reported. Titration or tapering: not reported. Duration of administration: not reported.
Yang et al[24]	China	41	Single center	January 2012 to January 2014	Sepsis-2	Esmolol vs none	Hemodynamic parameters including MAP, CVP, HR, CO, CI, SVI, and SVRI, and tissue oxygenation parameters including $ScvO_2$, lactic acid level, and troponin I	Administration of esmolol: initiated after randomization that was performed after 6-h resuscitation with fluid and vasopressors. Initial does of esmolol: 0.05 mg/kg/min. Titration of tapering: adjusted to achieve HR of $<$ 100 beats/min in 2 h. Duration of administration: not reported.
Morelli et al[22]	Italy	154	Single center	November 2010 to July 2012	Sepsis-2	Esmolol vs none	Reduction in HR to 80-94 beats/min over a 96-h period (28-d mortality, hemodynamic and organ function markers, norepinephrine dosages, and adverse events)	Administration of esmolol: initiated after randomization that was performed after resuscitation with fluid and vasopressors for 24 h. Initial dose of esmolol: initiated at 25 mg/h.

(Continued)

TABLE 1] (Continued)

Study	Country	Sample Size	Setting	Study Period	Definition of Sepsis	Intervention	Primary Outcome (Secondary Outcome)	Administration of Esmolol/Landiolol
								Titration or tapering: by ≥ 50 mg/h slowly every 20 min to reach HR between 80 and 94 beats/min within 12 h. Duration of administration: esmolol was continued until ICU discharge or death. Permitted maximum dose was 2,000 mg/h.

Afib = atrial fibrillation; APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; $ScvO_2$ = mixed venous oxygen saturation; SOFA = Sequential Organ Failure Assessment; SVI = stroke volume index; SVRI = systemic vascular resistance index.
[a]Authors did not specify primary outcomes and secondary outcomes.
[b]We contacted authors to ascertain whether the dose of esmolol was correct, but did not receive a response.

Results

Literature Search

Our search returned 978 articles. After removing the duplicates, 943 articles were screened. After screening the titles and abstracts, we excluded 901 obviously irrelevant articles (eg, studies not dealing with sepsis). Among the remaining 42 articles, full texts of which were reviewed, 10 were letter/commentary/editorial articles, eight were narrative reviews, seven were protocols, four were single-arm studies, four were case reports/series, one was a cohort study, one was an animal study, and two examined different medications; all of these studies were subsequently excluded.

Seven RCTs with a pooled sample size of 613 patients were finally included in our meta-analysis.[18-24] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection is shown in Figure 1. Study characteristics are summarized in Table 1. The sample size ranged from 41 to 154. Of the seven trials, six trials reported 28-day mortality[18-23] and the remaining trial investigated only hemodynamic and tissue oxygenation parameters,[24] as shown in Table 1. Five trials were single-center RCTs conducted in China,[18-21,24] one was a single-center RCT conducted in Italy,[22] and the remaining trial was a multicenter RCT conducted in Japan.[23] Sepsis and septic shock were diagnosed based on the Sepsis-2 definition in six studies[18-22,24] and the Sepsis-3 definition in one study.[23] The dose regimens of esmolol and landiolol were defined in each article. Six trials were open-label, and the control groups were administered standard treatment for sepsis without placebo,[18,19,21-24] whereas the remaining trial was double-blinded.[20] The follow-up period was 28 days in all six trials that reported 28-day mortality. The characteristics of the included patients, sources of infection, and inclusion and exclusion criteria of each study are summarized in Table 2, e-Table 2, and e-Table 3, respectively. The reported mean/median age of participants ranged from 34 to 69 years, and 50.7% to 70.1% were men. The mean APACHE II score ranged from 15.7 to 23.1. The mean/median norepinephrine dose at baseline ranged from 0.2 to 1.06 μg/kg/min. The inclusion criteria included the necessity of catecholamine use to maintain an MAP of ≥ 65 mm Hg in five studies,[18-20,22,23] HR ≥ 95 beats/min after adequate fluid resuscitation in three studies,[18,19,22] and HR > 100 beats/min after adequate fluid resuscitation in two studies.[21,23]

Risk of Bias

We evaluated the risk of bias in each of the seven RCTs, and the details are shown in the risk of bias summary (e-Fig 1) and risk of bias graph (e-Fig 2). All seven studies were considered low risk for random sequence generation (selection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Three studies[21-23] were considered low risk for allocation concealment (selection bias), which could not be assessed in the other four studies[18-20,24] because of a lack of information. One study[20] was considered low risk and four studies[19,21-23] were considered high risk for blinding of participants and personnel (performance bias). We were unable to assess the blinding of participants and personnel in the other two studies[18,24] because of a lack of information. Three studies[19,22,23] were considered high risk and one study[21] was considered low risk for blinding of outcome assessment; we were unable to assess the blinding of outcome assessment in the three other studies[18,20,24] because of a lack of information. Regarding other biases, one study[23] was considered low risk because it was conducted at multiple centers, and the remaining six studies[18-22,24] were considered high risk because they were conducted at a single center.

Primary Outcomes

Six out of seven RCTs with 572 patients reported 28-day mortality as shown in Figure 2. The use of ultrashort-acting β-blockers, esmolol or landiolol, in patients with sepsis and septic shock was significantly associated with a lower 28-day mortality (RR, 0.68; 95% CI, 0.54-0.85; $P < .001$). Unimportant heterogeneity was observed ($I^2 = 31\%$). The ARR and NNT to prevent one death were 18.2% and 5.5, respectively.

Secondary Outcome

All seven studies reported the lactic acid level at baseline and 24 h after enrollment. There were no significant differences between the esmolol/landiolol and control groups at baseline and 24 h after enrollment (SMD, −0.04; 95% CI, −0.21 to 0.13; SMD, 0.13; 95% CI, −0.37 to 0.63, respectively). Six studies reported the lactic acid level at 48 and 72 h after enrollment.[18,19,21-24] There was no significant difference in the lactic acid level at 48 h, but there was a significant difference in the lactic acid level at 72 h between the esmolol/landiolol and control groups in these studies (SMD, −0.42; 95% CI, −1.85 to 0.01; SMD, −0.45; 95% CI, −0.59 to −0.32, respectively). Forest plots of each point are shown in e-Figure 3.

Seven articles reported HR at 24 h after enrollment,[18-24] and there was a significant reduction in HR in the esmolol/landiolol group (SMD, −1.99; 95% CI, −2.99 to −0.99). Six studies reported MAP at 24 h after enrollment,[18-20,22-24] with no significant difference between the esmolol/landiolol and control groups (SMD, −0.11; 95% CI, −0.33 to 0.12). Four studies reported norepinephrine dose at 24 h after enrollment,[19,21-23] with no significant difference between the esmolol/landiolol and control groups (SMD, 0.10; 95% CI, −0.08 to 0.29). Five studies reported the cardiac index at 24 h after enrollment,[18-20,22,24] with no significant difference between the esmolol/landiolol and control groups (SMD, −0.16; 95% CI, −0.63 to 0.31). Five studies reported SVI at 24 h after enrollment,[18-20,22,24] and it was significantly higher in the esmolol/landiolol group than in the control groups (SMD, 0.26; 95% CI, 0.03-0.49). Four studies reported WBC count at 24 h after enrollment,[20-23] and the WBC count was significantly lower in the esmolol/landiolol group than in the control groups (SMD, −0.19; 95% CI, −0.37 to −0.01). Forest plots of these parameters are shown in Figure 3.

Sensitivity Analysis

Analyses of the subgroups in which the mortality rate of the control groups was $< 66\%$ and $\geq 66\%$ showed significantly lower 28-day mortality (RR, 0.59; 95% CI, 0.38-0.91; RR, 0.71; 95% CI, 0.53-0.95, respectively) (e-Fig 4). Furthermore, analyses of the subgroups in which sample size was < 100 and ≥ 100 showed significantly lower 28-day mortality (RR, 0.59; 95% CI, 0.41-0.85; RR, 0.72; 95% CI, 0.53-0.98, respectively) (e-Fig 5). We observed consistent results in these sensitivity analyses, which supports the robustness of the significant association between the use of ultrashort-acting β-blockers and 28-day mortality.

Publication Bias

We detected no evidence of publication bias when assessing funnel plots visually (e-Fig 6). We also statistically assessed publication bias using Begg rank correlation test ($P \geq .999$) and Egger linear regression test ($P = .554$).

Discussion

This study was a systematic review and meta-analysis on the use of β-blockers including esmolol and landiolol for the treatment of patients with sepsis and septic shock with tachycardia. Seven RCTs were included in the analysis. The use of ultrashort-acting

TABLE 2] Characteristics of the Included Patients

Study		Age, y	Men, %	APACHE II Score	Norepinephrine Dose at Baseline, μg/kg/min	28-d Mortality[a]
Kakihana et al[23]	Landiolol	67.8 ± 13.8	68.4	23.1 ± 8.9	0.2 ± 0.2	9/75 (12)
	Control	66.4 ± 15.2	50.7	22.2 ± 8.6	0.2 ± 0.2	15/75 (20)
Liu et al[21]	Esmolol	58.0 ± 15.0	58.0	18.8 ± 6.5	1.06 ± 1.43	31/50 (62.0)
	Control	57.0 ± 18.0	56.0	19.1 ± 7.5	0.76 ± 0.79	34/50 (68.0)
Wang et al[20]	Esmolol	67.2 ± 12.5	70.0	18.4 ± 6.3	Not reported	9/30 (30/0)
	Control	62.5 ± 14.5	60.0	15.7 ± 6.3	Not reported	11/30 (36.7)
Xinqiang et al[18]	Esmolol	61.4 ± 6.9	58.3	20.8 ± 3.1	0.38 ± 0.04	6/24 (25.0)
	Control	61.2 ± 6.4	54.2	21.2 ± 2.7	0.39 ± 0.04	15/24 (62.5)
Wang et al[19]	Esmolol	34 (21-60)[b]	63.3	21.2 ± 5.7	0.25 ± 0.16	12/30 (40.0)
	Control	38 (20-57)[b]	63.3	20.8 ± 5.6	0.28 ± 0.21	20/30 (66.7)
Yang et al[24]	Esmolol	51.0 ± 22.6	Not reported	20.1 ± 9.2	Not reported	Not reported
	Control	55.0 ± 25.4	Not reported	21.3 ± 8.3	Not reported	Not reported
Morelli et al[22]	Esmolol	66 (52-75)[c]	70.1	Not reported	0.38 (0.21-0.87)[d]	38/77 (49.4)
	Control	69 (58-78)[c]	68.8	Not reported	0.40 (0.18-0.71)[d]	62/77 (80.5)

Values are reported as mean ± SD or as otherwise indicated. APACHE II = Acute Physiology and Chronic Health Evaluation II.
[a]Values are No. of participants/total No. of participants (%).
[b]Age is reported as median (range).
[c]Age is reported as median (interquartile range).
[d]Norepinephrine dose at baseline is reported as median (interquartile range).

b-blockers, esmolol or landiolol, in patients with sepsis and septic shock was associated with significantly lower 28-day mortality, with an RR of 0.68, ARR of 0.18, and NNT of 5.5. In this study, the inclusion criteria in most of the included studies were tachycardia with HR > 95 to 100 beats/min despite adequate initial resuscitation that ranged from 6 to 24 h. Hence, the indication of esmolol or landiolol should include the presence of persistent tachycardia despite adequate initial resuscitation.

The Surviving Sepsis Campaign guidelines[25] suggest the use of α- and β-agonists including norepinephrine and dobutamine for hemodynamic management if patients have hypotension or hypoperfusion. In this context, the use of β-blockers seems to be paradoxical. In fact, β-blockers have been classically contraindicated in patients with septic shock because of their negative chronotropic, inotropic, and vasodilatory effects.

Geri et al[26] reported the clustering approach on a large database to distinguish cardiovascular phenotypes in patients with septic shock and revealed that patients with left ventricular systolic dysfunction had the worst mortality compared with the ones with other phenotypes, including right ventricular failure, hyperkinetic state, persistent hypovolemia, and with well-resuscitated patients without cardiac dysfunction. This suggests the importance of improving cardiovascular efficiency and cardioprotective strategy in

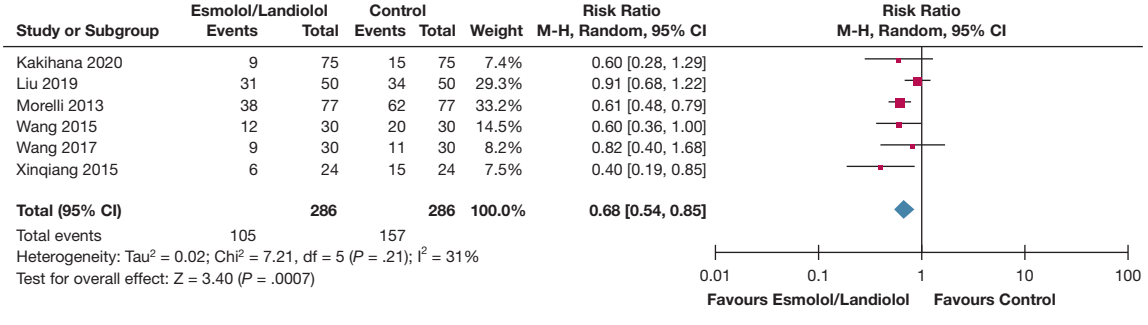
Esmolol/Landiolol
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Kakihana 2020 9 75 15 75 7.4% 0.60 [0.28, 1.29]
Liu 2019 31 50 34 50 29.3% 0.91 [0.68, 1.22]
Morelli 2013 38 77 62 77 33.2% 0.61 [0.48, 0.79]
Wang 2015 12 30 20 30 14.5% 0.60 [0.36, 1.00]
Wang 2017 9 30 11 30 8.2% 0.82 [0.40, 1.68]
Xinqiang 2015 6 24 15 24 7.5% 0.40 [0.19, 0.85]
Total (95% CI) 286 286 100.0% 0.68 [0.54, 0.85]
Total events 105 157
Heterogeneity: Tau² = 0.02; Chi² = 7.21, df = 5 (P = .21); I² = 31%
Test for overall effect: Z = 3.40 (P = .0007)
0.01 0.1 1 10 100
Favours Esmolol/Landiolol
Favours Control

Figure 2 – *Forest plot of esmolol or landiolol group vs control group: all-cause mortality at 28 d. M-H = Mantel-Haenszel.*

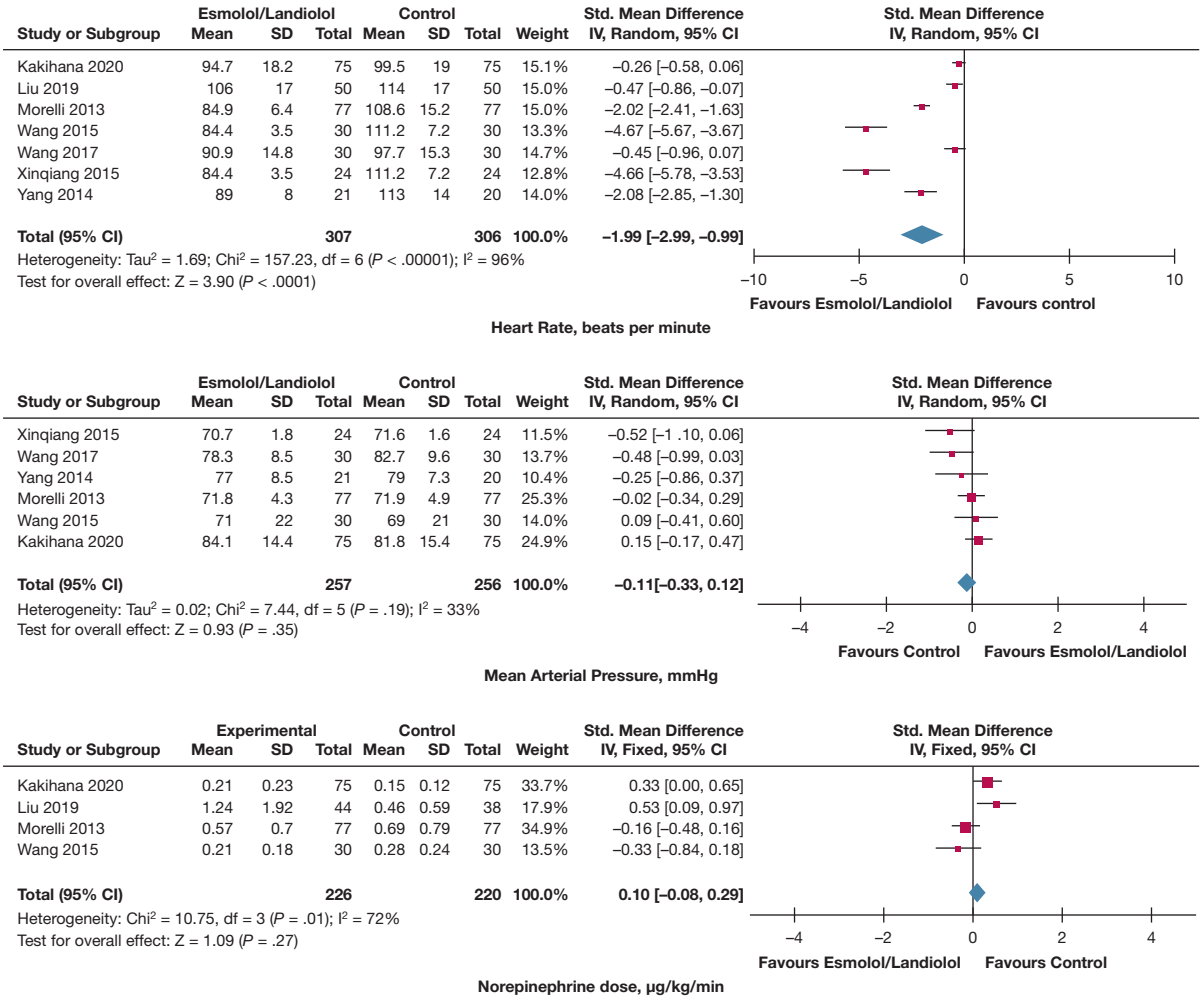
Esmolol/Landiolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Kakihana 2020 94.7 18.2 75 99.5 19 75 15.1% −0.26 [−0.58, 0.06]
Liu 2019 106 17 50 114 17 50 15.0% −0.47 [−0.86, −0.07]
Morelli 2013 84.9 6.4 77 108.6 15.2 77 15.0% −2.02 [−2.41, −1.63]
Wang 2015 84.4 3.5 30 111.2 7.2 30 13.3% −4.67 [−5.67, −3.67]
Wang 2017 90.9 14.8 30 97.7 15.3 30 14.7% −0.45 [−0.96, 0.07]
Xinqiang 2015 84.4 3.5 24 111.2 7.2 24 12.8% −4.66 [−5.78, −3.53]
Yang 2014 89 8 21 113 14 20 14.0% −2.08 [−2.85, −1.30]
Total (95% CI) 307 306 100.0% −1.99 [−2.99, −0.99]
Heterogeneity: Tau² = 1.69; Chi² = 157.23, df = 6 (P < .00001); I² = 96%
Test for overall effect: Z = 3.90 (P < .0001)
−10 −5 0 5 10
Favours Esmolol/Landiolol
Favours control
Heart Rate, beats per minute
Esmolol/Landiolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Xinqiang 2015 70.7 1.8 24 71.6 1.6 24 11.5% −0.52 [−1 .10, 0.06]
Wang 2017 78.3 8.5 30 82.7 9.6 30 13.7% −0.48 [−0.99, 0.03]
Yang 2014 77 8.5 21 79 7.3 20 10.4% −0.25 [−0.86, 0.37]
Morelli 2013 71.8 4.3 77 71.9 4.9 77 25.3% −0.02 [−0.34, 0.29]
Wang 2015 71 22 30 69 21 30 14.0% 0.09 [−0.41, 0.60]
Kakihana 2020 84.1 14.4 75 81.8 15.4 75 24.9% 0.15 [−0.17, 0.47]
Total (95% CI) 257 256 100.0% −0.11[−0.33, 0.12]
Heterogeneity: Tau² = 0.02; Chi² = 7.44, df = 5 (P = .19); I² = 33%
Test for overall effect: Z = 0.93 (P = .35)
−4 −2 0 2 4
Favours Control
Favours Esmolol/Landiolol
Mean Arterial Pressure, mmHg
Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Kakihana 2020 0.21 0.23 75 0.15 0.12 75 33.7% 0.33 [0.00, 0.65]
Liu 2019 1.24 1.92 44 0.46 0.59 38 17.9% 0.53 [0.09, 0.97]
Morelli 2013 0.57 0.7 77 0.69 0.79 77 34.9% −0.16 [−0.48, 0.16]
Wang 2015 0.21 0.18 30 0.28 0.24 30 13.5% −0.33 [−0.84, 0.18]
Total (95% CI) 226 220 100.0% 0.10 [−0.08, 0.29]
Heterogeneity: Chi² = 10.75, df = 3 (P = .01); I² = 72%
Test for overall effect: Z = 1.09 (P = .27)
−4 −2 0 2 4
Favours Esmolol/Landiolol
Favours Control
Norepinephrine dose, µg/kg/min

Figure 3 – *Forest plot of esmolol or landiolol group vs control group: cardiac index, heart rate, mean arterial pressure, norepinephrine dose, stroke volume index, and WBC count at 24 h after enrollment. IV = inverse variance; Std. = standardized.*

patients with sepsis. Morelli et al[27] reported that HR reduction with esmolol effectively improved cardiovascular efficiency by decreasing the static arterial elastance and increasing the stroke volume. In our study, there were no significant differences between the esmolol/landiolol and control groups in cardiac index, MAP, and norepinephrine dosage at 24 h after enrollment, whereas the use of esmolol/landiolol was associated with significantly lower HR. This might be because of significantly higher SVI in the esmolol/landiolol group. These findings suggest that the use of esmolol or landiolol might be beneficial in reducing HR to improve cardiovascular efficiency in patients with sepsis with persistent tachycardia despite initial resuscitation.

In addition to the aforementioned hemodynamic effects of β-blockers, the mechanism underlying the beneficial effects of β-blockers is considered multidimensional and involves the normalization of the hypermetabolic state and immune modulation.[6] Although most of these effects were reported in experimental settings, our study suggests that the use of esmolol or landiolol in patients with sepsis and septic shock was associated with a significantly better clearance of lactic acid over time and a significantly lower WBC count at 24 h. These results support the multidimensional effects of β-blockers and imply that overactivation of β-adrenergic receptors might worsen outcomes. The use of epinephrine and dobutamine in patients with septic shock has been reported to be associated with significantly higher in-hospital mortality.[28] This harmful effect of the overactivation of β-adrenergic receptors has been suggested even in patients with cardiogenic shock[29-31]; however, it is thought that β-adrenergic receptors are necessary to manage cardiogenic shock.

In this systematic review, the 28-day mortality was significantly lower with marked RR and NNT. Given

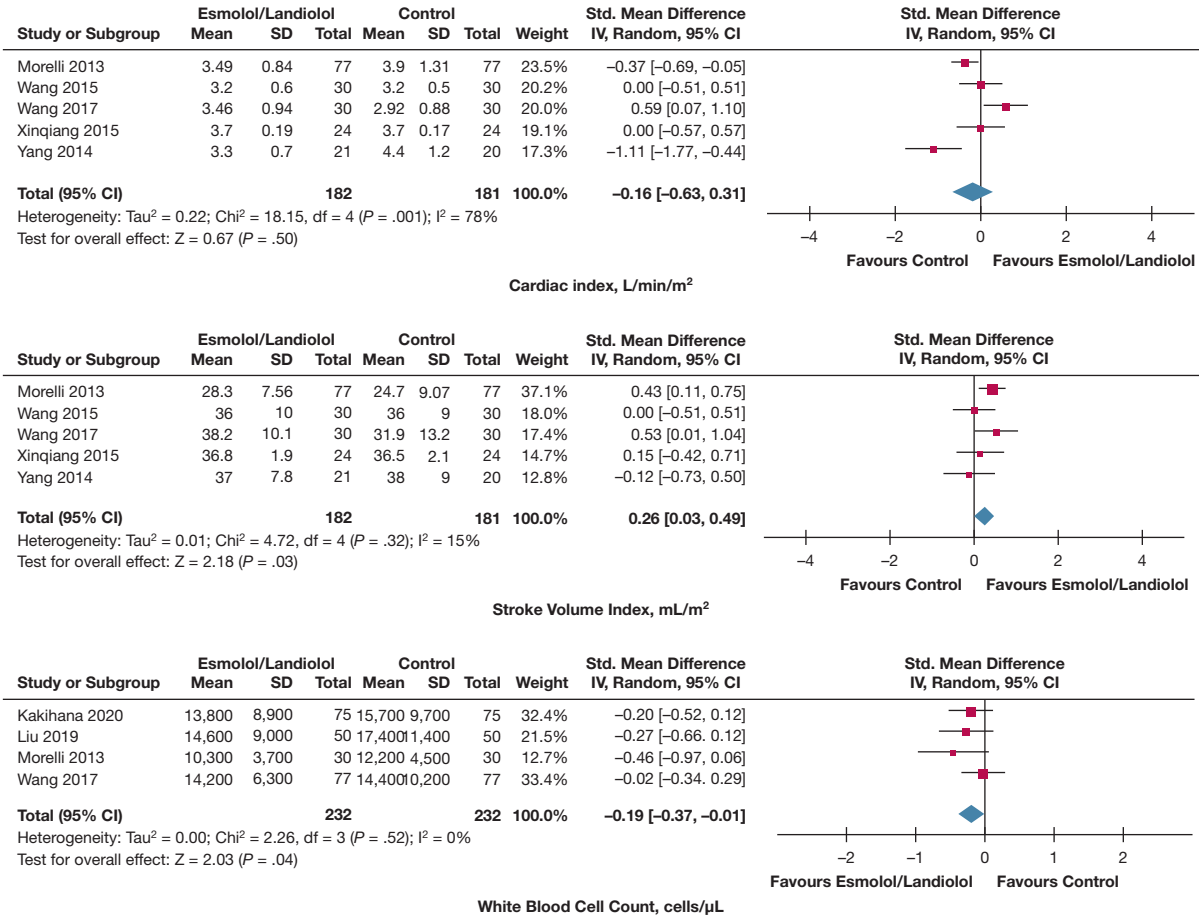
Esmolol/Landiolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Morelli 2013 3.49 0.84 77 3.9 1.31 77 23.5% −0.37 [−0.69, −0.05]
Wang 2015 3.2 0.6 30 3.2 0.5 30 20.2% 0.00 [−0.51, 0.51]
Wang 2017 3.46 0.94 30 2.92 0.88 30 20.0% 0.59 [0.07, 1.10]
Xinqiang 2015 3.7 0.19 24 3.7 0.17 24 19.1% 0.00 [−0.57, 0.57]
Yang 2014 3.3 0.7 21 4.4 1.2 20 17.3% −1.11 [−1.77, −0.44]
Total (95% CI) 182 181 100.0% −0.16 [−0.63, 0.31]
Heterogeneity: Tau² = 0.22; Chi² = 18.15, df = 4 (P = .001); I² = 78%
Test for overall effect: Z = 0.67 (P = .50)
−4 −2 0 2 4
Favours Control Favours Esmolol/Landiolol
Cardiac index, L/min/m²
Esmolol/Landiolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Morelli 2013 28.3 7.56 77 24.7 9.07 77 37.1% 0.43 [0.11, 0.75]
Wang 2015 36 10 30 36 9 30 18.0% 0.00 [−0.51, 0.51]
Wang 2017 38.2 10.1 30 31.9 13.2 30 17.4% 0.53 [0.01, 1.04]
Xinqiang 2015 36.8 1.9 24 36.5 2.1 24 14.7% 0.15 [−0.42, 0.71]
Yang 2014 37 7.8 21 38 9 20 12.8% −0.12 [−0.73, 0.50]
Total (95% CI) 182 181 100.0% 0.26 [0.03, 0.49]
Heterogeneity: Tau² = 0.01; Chi² = 4.72, df = 4 (P = .32); I² = 15%
Test for overall effect: Z = 2.18 (P = .03)
−4 −2 0 2 4
Favours Control Favours Esmolol/Landiolol
Stroke Volume Index, mL/m²
Esmolol/Landiolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Kakihana 2020 13,800 8,900 75 15,700 9,700 75 32.4% −0.20 [−0.52, 0.12]
Liu 2019 14,600 9,000 50 17,400 11,400 50 21.5% −0.27 [−0.66. 0.12]
Morelli 2013 10,300 3,700 30 12,200 4,500 30 12.7% −0.46 [−0.97, 0.06]
Wang 2017 14,200 6,300 77 14,400 10,200 77 33.4% −0.02 [−0.34. 0.29]
Total (95% CI) 232 232 100.0% −0.19 [−0.37, −0.01]
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 3 (P = .52); I² = 0%
Test for overall effect: Z = 2.03 (P = .04)
−2 −1 0 1 2
Favours Esmolol/Landiolol Favours Control
White Blood Cell Count, cells/μL

Figure 3 – *continued*

that both basic and clinical studies support the use of β-blockers in patients with septic shock and tachycardia, the present study should have a significant effect on the future direction of further clinical studies.

A major concern regarding the use of β1-blockers for sepsis is the possible reduction in cardiac output, which can lead to hypotension. Contrarily, Morelli et al[32] reported that HR reduction by esmolol could be achieved safely in patients with sepsis with noncompensatory tachycardia, whereas pharmacologic HR reduction in compensatory tachycardia for a state of reduced left ventricular contractility could be a risk for hemodynamic deterioration. In our meta-analysis, most of the included trials included patients with sepsis with noncompensatory tachycardia (ie, persistent tachycardia despite initial resuscitation). In fact, there were no significant differences in the MAP, dose of norepinephrine, and cardiac index between the esmolol/landiolol and control groups, and SVI was significantly higher in the esmolol/landiolol groups at 24 h after enrollment. In this meta-analysis, CI and SVI were monitored in five studies, and the method of titration of ultrashort-acting β-blockers was well defined, suggesting that close monitoring and a well-defined protocol of β-blocker titration helps in the safe use of ultrashort-acting β-blockers in patients with sepsis with noncompensatory tachycardia. However, most of the included studies excluded patients with cardiac dysfunction, patients who received inadequate fluid resuscitation, and patients without tachycardia, and it remains unclear whether the use of ultrashort-acting β-blockers is safe in such populations.

There were some limitations to this systematic review and meta-analysis. First, the total number of included patients in this study was relatively small, and the generalizability of the findings remains debatable. Second, the primary outcomes of most of the included studies were HR reduction in patients with sepsis with persistent tachycardia, and it may still be controversial whether the mortality benefit is caused by HR reduction or by the β-blockers. However, a previous propensity score-matched analysis showed that

b-blockers were associated with improved survival compared with other rate-controlling medications in patients with sepsis complicated by atrial fibrillation.[33] This suggests the superiority of β-blockers in terms of the effect on mortality in patients with sepsis. Third, the duration of administration of these β-blockers and the severity, such as APACHE II score or baseline norepinephrine dose, differed among the included studies, and these differences might have affected the main outcome. Finally, six out of the seven included RCTs were conducted in Asia and most of the included patients were assumed to be of Asian ethnicity. Therefore, validation with larger trials including other ethnicities is warranted, and two clinical trials were ongoing in Europe at the time of drafting this article (EudraCT Nos. 2017-002138-22[34] and 2017-001785-14).

This systematic review and meta-analysis suggested that esmolol or landiolol use in patients with persistent tachycardia despite initial resuscitation was associated with significantly lower 28-day mortality.

Acknowledgments

Author contributions: D. H. and R. S. are the guarantors of this work and as such have full access to all data in the study and take responsibility for the integrity of data and the accuracy of data analysis. D. H. and R. S. are equally responsible for the conception of the study, collection and analysis of data, interpretation of data, writing of the draft manuscript, and critical revision of the manuscript. N. P. substantially contributed to the collection of data. K. N. and K. T. substantially contributed to the analysis and interpretation of data. T. Y. and O. N. supervised the drafting and revision of the manuscript. All authors approved the submission of the final manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: O. N. received research grants and consulting fees from Ono Pharmaceutical Co, Ltd and research grants from Maruishi Pharmaceutical Co, Ltd; Fuso Pharmaceutical Industries; Japan Blood Products Organization; and Asahi Kasei Pharma Corp. None declared (D. H., R. S., N. P., K. N., K. T., T. Y.).

Other contributions: We thank Dr Andrea Morelli, MD, and Dr Sun Tongwen, MD, PhD, for sharing the data of their RCTs.

Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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